Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis

C Nederstigt[1,2], B S Uitbeijerse[3,*], L G M Janssen[1,*], E P M Corssmit[1], E J P de Koning[1,3] and **O M Dekkers[1,2,4]**

[1]Department of Internal Medicine, Section Endocrinology & Metabolism, [2]Department of Clinical Epidemiology, [3]Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands, and [4]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

*(B S Uitbeijerse and L G M Janssen contributed equally to this work)

Correspondence should be addressed to C Nederstigt
Email
c.nederstigt@lumc.nl

Abstract

Introduction: The association between type 1 diabetes (T1D) and other auto-immune diseases is well known. However, a quantitative overview of all associated auto-immune diseases and their prevalence in T1D is lacking.
Methods: We searched PubMed, Web of Science, EMBASE and Cochrane library in September 2018 to identify relevant articles about the prevalence of the following associated auto-immune diseases in T1D cohorts: auto-immune thyroid disease, celiac disease, gastric autoimmunity including pernicious anemia, vitiligo and adrenal gland insufficiency. A meta-analysis was performed to estimate pooled prevalence using a random-effects model. Furthermore, random-effects meta-regression analysis was performed to assess the association between prevalence and mean age or diabetes duration.
Results: One hundred eighty articles were eligible including a total of 293 889 type 1 diabetes patients. Hypothyroidism (65 studies) was prevalent in 9.8% (95% CI: 7.5–12.3) of patients. Meta-regression showed that for every 10-year age increase, hypothyroidism prevalence increased 4.6% (95% CI: 2.6–6.6, $P < 0.000$, 54 studies). Weighted prevalence of celiac disease was 4.5% (95% CI: 4.0–5.5, 87 studies). Gastric autoimmunity was found in 4.3% of patients (95% CI: 1.6–8.2, 8 studies) and vitiligo in 2.4% (95% CI: 1.2–3.9, 14 studies) of patients. The prevalence of adrenal insufficiency was 0.2% (95% CI: 0.0–0.4, 14 studies) and hyperthyroidism was found in 1.3 percent (95% CI: 0.9–1.8, 45 studies) of type 1 diabetes patients. For all analyses, statistical heterogeneity between studies was moderate to high.
Conclusions: The prevalence of antibody-mediated auto-immune disease is high among type 1 diabetes patients. Especially hypothyroidism and celiac disease are frequently found.

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Introduction

Type 1 diabetes is an endocrine disorder characterized by the destruction of insulin-producing pancreatic beta cells, in which T cells play a central role (1, 2, 3). Type 1 diabetes patients have a higher risk of other auto-immune diseases, in particular thyroid diseases and celiac disease (4, 5, 6). Associated antibodies are also frequently found among these patients, sometimes coinciding with overt, but often subclinical disease (7, 8). Moreover, it was shown that type 1 diabetes patients have more gastric autoimmunity, vitiligo and adrenal gland insufficiency (9, 10, 11, 12, 13, 14, 15, 16, 17). It was shown that the pathogenesis of these diseases share common genetic factors and immunologic processes, key to the etiology of the disease (18, 19, 20, 21, 22).

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Concomitant auto-immune disease in type 1 diabetes patients not only can complicate diabetes management (23, 24) but also can lead to varying clinical symptoms, ranging from minor complaints up till potential life-threatening situations in case of adrenal insufficiency (25, 26). Thus, substantiated estimates of risk of auto-immune disease followed by the development of optimal screening and treatment strategies is important for type 1 diabetes patients, also contributing to better glucose regulation and quality of life (27, 28).

An increased prevalence of concomitant auto-immune diseases in type 1 diabetes has often been reported but a complete overview is lacking. The aim of the present systematic review and meta-analysis is to provide a quantitative overview of the prevalence of associated auto-immune diseases in type 1 diabetes patients, thereby contributing to the knowledge base of screening polices in these patients.

Methods

Data sources and searches

We searched PubMed, Web of Science, EMBASE and Cochrane library in September 2018 to identify potentially relevant articles reporting prevalence of associated auto-immune disease (AAID) – auto-immune thyroid disease (AITD) including hypo- and hyperthyroidism, celiac disease (CD), gastric autoimmunity (GAI) including pernicious anemia, vitiligo and adrenal gland insufficiency (AGI) – in patients with type 1 diabetes.

For AITD, CD, AGI and GAI, only studies published from 1999 onward were eligible, because in that period commercial kits for the measurement of antibodies became widely available (29, 30, 31, 32, 33, 34, 35). As vitiligo is a clinical diagnosis independent of laboratory measurements, studies were eligible irrespective of the year of publication. The search strategy was drafted in collaboration with a trained librarian and is shown in the Supplementary Table 3 (see section on supplementary data given at the end of this article). Reference lists of included studies where checked for additional references. Only studies in English, Dutch, French and German were considered.

Study selection

Title and abstract of articles retrieved from the search strategy were initially screened by one reviewer (C N) for eligibility. Potentially relevant articles were read in full-text by one reviewer (C N, B U or L J), followed by data extraction based on a predefined data extraction sheet (see Supplementary Table 4). Eligibility and extracted data were verified by a second reviewer (C N, B U or L J), and disagreement was resolved by consensus. In case of multiple studies describing the same cohort of patients, the study with the largest sample size was included, unless a smaller study included more relevant patient characteristics.

Cohort studies and cross-sectional studies that investigated prevalence or (cumulative) incidence of AAID in T1D patients were potentially eligible. Study designs (case–control studies, case series) that disable the calculation of absolute risks were not included (36). Studies excluding an unknown number of patients with the outcome of interest at baseline were also excluded, as prevalence could then not be calculated. Studies based on specific subgroups of T1D diabetes patients only, other than selected on age or gender, were excluded. In case of follow-up studies, we extracted prevalence at the end of the study period, unless loss to follow-up was considerable.

Data extraction

From included studies, we extracted prevalence of AITD, CD, gastric autoimmunity, vitiligo and adrenal gland insufficiency and/or prevalence of autoantibodies corresponding with one of above-mentioned diseases. For definition of the diseases, we relied on the criteria used by the authors of included studies. Details of definitions in use are provided in the Supplementary Table 5. Additionally, we extracted information about patient characteristics of the study populations, for example, prevalence of autoantibodies including anti-GAD, age, duration of diabetes and age at diabetes onset.

Furthermore, we registered definitions of diseases, diagnostic criteria and laboratory assays that were used in the studies (data extraction sheet, Supplementary Table 4).

Quality assessment

The present meta-analysis is based on observational studies. Risk of bias assessment was based on design elements that potentially bias the studied association between diabetes and the auto-immune diseases under study. The following elements were considered:

1. Selection of patients: selection of consecutive patients (or a random sample) of a predefined type 1 diabetes population was considered adequate. Other selection criteria are considered as intermediate or high risk of bias depending on the method.

2. Type 1 diabetes definition: diagnosis following widely accepted criteria (e.g. (37, 38)) or based on clinical course in combination with associated auto-antibody positivity (anti-GAD) was considered as low risk of bias. Unclear or non-standardized diagnostic criteria were considered as high risk of bias.
3. Screening for concomitant auto-immune disease: Screening at inclusion of the study or at fixed intervals (independent of the risk of outcome) is considered as low risk of bias, screening based on antibody positivity is considered as intermediate risk of bias. Screening based on clinical suspicion only is considered as high risk of bias as this will underestimate the prevalence.
4. Screening for antibodies: Screening at inclusion in the study or at fixed intervals is considered as low risk of bias, screening at random was considered as intermediate risk of bias. Screening based on clinical suspicion is considered as high risk of bias.

Analysis

The main outcome was the pooled percentage of type 1 diabetes patients with any of the studied AAIDs. Most studies provided number of patients with AAID or report percentages. Prevalence of individual studies was calculated as number of patients with the outcome divided by the total number of diabetes patients at risk. For meta-analysis we used the metaprop command as described by Nyaga *et al.* (39). For assessment and description of heterogeneity the I^2 statistics was used.

Meta-regression analyses were performed with an exact likelihood approach in a random-effects model to test for an association of auto-immune diseases prevalence with age and duration of diabetes (if provided) using study level summary data. Meta-regression was not performed in case of <10 studies.

All analyses were performed with STATA 14.0 (Stata Corp.).

Results

The initial search yielded 1515 publications, of which 885 were excluded based on title and abstract. Of the remaining articles, 380 studies were retrieved for further evaluation. The main reasons for exclusion were year of publication, inapplicable inclusion criteria for patient selection and excluding an unknown number of patients with the outcome of interest at baseline (Fig. 1). Finally, 180 studies were included.

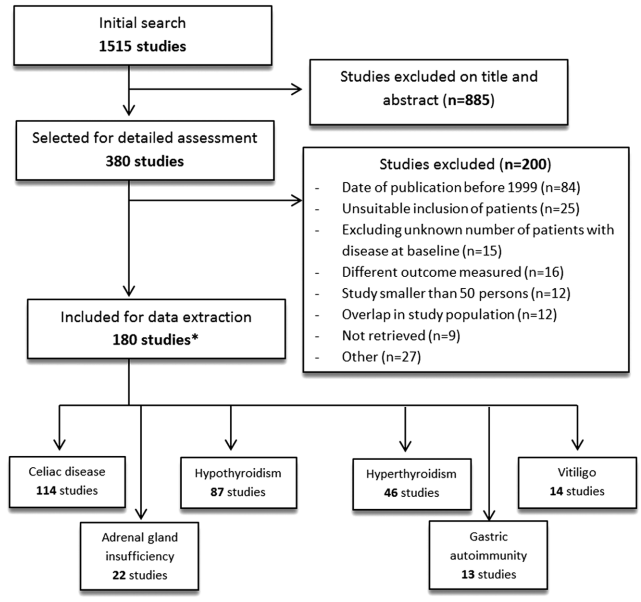

Figure 1
Flow-chart of study selection.

Study characteristics

Details of the 180 included studies are summarized in the Supplementary Table 6. Included studies were published from 1998 to 2018. From 180 studies, data about one auto-immune disease or a related antibody was extracted, and in the other studies, prevalence of more than one auto-immune disease or antibody was reported (maximum 6). The 180 studies comprised 293 889 patients in total. The mean age of the study populations was 19.2 years (range 3.2 to 64.4) and the age at onset of diabetes was 12.2 years (range 4.4 to 53.8).

Risk of bias assessment

Overall, inclusion criteria and screening methods were poorly reported. Only 13 studies (7%) reported information on all eligibility criteria. Detailed information on the risk of bias of the studies is provided in Supplementary Table 7.

Prevalence of associated disease and auto-antibodies

The number of studies that provided data for specific auto-immune conditions ranged from 87 (CD) to 8 (gastric autoimmunity) and for associated antibodies from 4 to 49. An overview of weighted prevalence of associated diseases and auto-antibodies are shown in Table 1.

Table 1 Meta-analysis of auto-immune disease and related antibodies among type I diabetes patients.

Disease of interest		Weighted mean prevalence (%)	95% CI	Studies included (*n*)	Reported prevalence in the general population (%)
Thyroid disease	Hypothyroidism	9.8	7.5–12.3	65	2–4.6 (40, 88)
	TPO and or TG antibodies	18.9	17.2–20.6	35	Unknown
	TPO antibodies	18.3	15.8–21.0	53	11.3–12.8 (40, 46)
	TG antibodies	12.3	10.0–14.9	29	10.4 (40)
	Hyperthyroidism	1.3	0.9–1.8	45	1.0–4.0 (40, 65, 66, 67)
	TSH receptor antibodies / TSI	9.5	1.4–22.7	4	Unknown
Celiac disease	Celiac disease	4.7	4.0–5.5	87	0.5–1.0 (73, 74, 89)
	Any gluten related antibodies	10.2	8.4–12.7	24	Unknown
	Tissue transglutaminase antibodies (IgA)	9.8	8.2–11.6	40	1.5 (90)
	Tissue transglutaminase antibodies (IgA/IgG)	9.8	8.4–11.3	49	2.1 (91)
	Anti-endomysial antibodies (IgA)	5.3	4.3–6.4	26	0.8 (92)
	Antigliadin antibodies (IgA)	9.7	5.1–15.5	13	1.6 (74)
	Antigliadin antibodies (IgG)	12.7	6.1–21.0	11	7.1 (74)
Gastric autoimmunity	Pernicious anemia	4.3	1.6–8.2	8	0.2 (79)
	Anti-parietal cell antibodies	9.3	5.4–14.1	7	3–10 (93)
Vitiligo	Vitiligo	2.4	1.2–3.9	14	0.4 (79)
Adrenal gland insufficiency	Adrenal gland insufficiency	0.2	0.0–0.4	15	0.012 (87)
	Anti-adrenal antibodies (AAA/21-OHab)	1.4	0.8–2.2	13	Unknown

Disease prevalence is also calculated for studies with a mean age under or over 25 years, see Supplementary Table 1. Details of relation with age or duration of diabetes in thyroid and CD are shown in Supplementary Table 2.

Thyroid disease

Hypothyroidism

In total, 65 studies reported the prevalence of hypothyroidism, which ranged from 0.6 and 44%. The pooled prevalence of hypothyroidism in T1D was 9.8% (95% CI: 6.5–12.3, I^2 99%) and of clinical overt hypothyroidism 3.5% (95% CI: 2.0–5.2, I^2 83%, 13 studies) (Fig.2). Meta-regression showed that for every 10-year increase in age, the prevalence of auto-immune hypothyroidism (including subclinical disease) increases with 4.6% (95% CI: 2.6–6/8, $P<0.000$, 54 studies). Also an association with diabetes duration was found, with an increase in prevalence of 8.8% every 10 years (95% CI: 5.4–12.2, $P<0.000$, 45 studies).

Hyperthyroidism

Reported prevalence of hyperthyroidism ranged between 0.0 and 7.5%; the weighted mean prevalence was 1.3% (95% CI: 0.9–1.8, I^2: 93%, 45 studies). Prevalence of hyperthyroidism was increasing with 0.5% with every 10-year increase of age (95% CI: 0.1–1.0, P 0.013, 34 studies) and with 1.3% with every 10-year increase in diabetes duration (95% CI: 0.5–2.1, P 0.003, 27 studies).

AITD-related antibodies

Prevalence of thyroid antibodies was 18.9% (95% CI: 17.2–20.6, I^2: 93%, 35 studies) for TPO, TG or both (Fig. 3) Weighted prevalence of TPO positivity was 18.3% (95% CI: 15.8–21.0, I^2: 92% 53 studies); TG antibody positivity 12.3% (95% CI: 10.0–14.9, I^2: 87%, 29 studies). Meta-regression analysis showed that for every 10-year increase of age, the prevalence of TPO antibodies increased with 3.5% (95% CI: 1.2–5.6, P 0.002, 49 studies) and 7.0% with 10-year increase in diabetes duration (95% CI: 1.2–12.9, P 0.020, 42 studies). Prevalence of TG antibodies was not clearly related to age or diabetes duration. Mean prevalence of TSH receptor antibody positivity in type 1 diabetes patients was 9.5% (95% CI: 1.4–22.7, I^2: 89%, 4 studies).

Celiac disease

Including 87 studies, prevalence of CD ranged from 0.4 up till 13.5%, mean 4.7% (95% CI: 4.0–5.5, I^2: 97%). The prevalence was not clearly related to age or duration of diabetes in a meta-regression. Pooled prevalence of autoantibodies varied from 5.3 to 12.7% depending on the type of antibody (Table 1). Meta-regression analysis showed that for every 10-year increase of age, the prevalence of

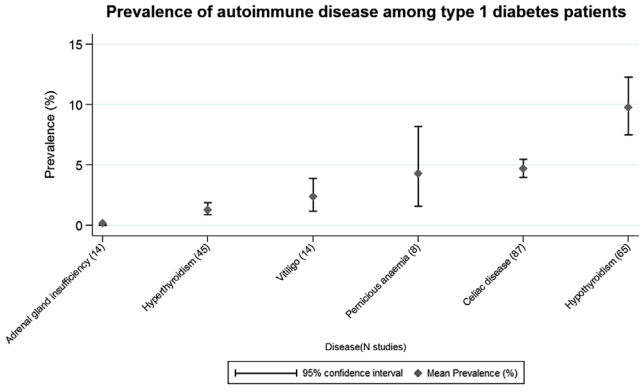

Figure 2
Overview of mean prevalence of auto-immune disease among type 1 diabetes patients.

any CD-associated antibody positivity increased with age and diabetes duration (6.8%, 95% CI: 0.2–13.3, *P* 0.043, 19 studies and 1.5%, 95% CI: –0.1, 30.7, *P* 0.051, 16 studies). However, prevalence varied depending on the type of antibody. Anti-endomysial antibody positivity decreased with 1.0% with 10 years of age (95% CI: –1.8 to –0.2, *P* 0.01, 24 studies) and prevalence of antigliadin antibodies (IgA) increased with diabetes duration (14.4% in 10 years, 1.4, 27.4, 10 studies). Prevalence of tissue transglutaminase antibodies was stable across age ranges.

Gastric autoimmunity

Mean prevalence of pernicious anemia was 4.3% (95% CI: 1.6–8.2, I^2: 93%, 8 studies). Anti-parietal cell antibodies were prevalent in 9.3% of the patients (95% CI: 5.4–14.1, I^2: 94%, 7 studies).

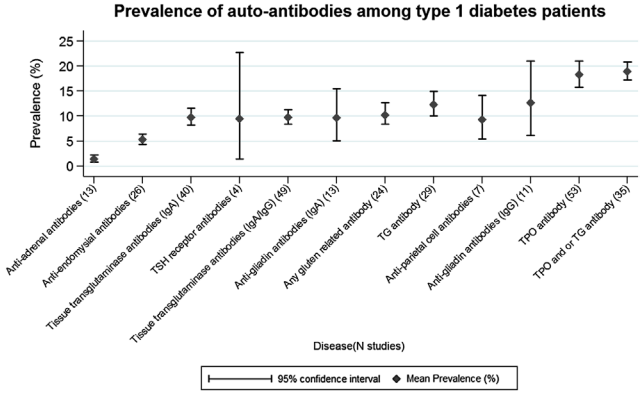

Figure 3
Overview of mean prevalence of auto-immune disease related antibodies among type 1 diabetes patients.

Vitiligo

Prevalence of vitiligo ranged from 0.5 to 23.3% and was found in 2.4% (95% CI: 1.2–3.9, I^2: 88%, 14 studies).

Adrenal gland insufficiency

Adrenal gland insufficiency was prevalent in 0–4% of the population (14 studies) with a mean prevalence of 0.2% (95% CI: 0.0–0.4, I^2: 43%). Mean prevalence of anti-adrenal antibody positivity in type 1 diabetes patients was 1.4% (95% CI: 0.8–2.2, I^2: 66%, 13 studies), with no relation with age.

Discussion

This meta-analysis provides a broad overview of concomitant auto-immune disease in type 1 diabetes patients. We found an increased prevalence for most of the diseases investigated compared to the general population and an increasing prevalence with age in thyroid disease (Table 1). The apparent lack of association between age and other auto-immune diseases may be due to a lack of power of an analysis at the study level. Individual patient data analysis may provide more insight in the association with age.

Thyroid disease

Hypothyroidism

In our study, we found a prevalence of hypothyroidism among type 1 diabetes patients twice as high as the general population (9.8 vs 4.6% (40)). Reported prevalence ranged from 0.6 to 44%, depending on the age of the study population. Also a geographical distribution may translate into prevalence differences, with an average higher prevalence in the southeast of Europe and some parts of Asia (41, 42, 43, 44, 45).

The prevalence of TPO antibodies is also higher among type 1 diabetes patients, 18.9 vs reported prevalence in the general population of 11.3–12.8% (40, 46), in contrast to TG antibodies, with a similar prevalence (12.3 vs 10.4 (40)). This suggests that TPO antibodies are more specific and more frequently present in patients with AITD (47).

Differences in reported prevalence between study populations may partly be explained by the mean age of the study population, as the prevalence is higher at older age (Supplementary Table 1). Although there is a high variability between diagnostic criteria used, laboratory

measurements and reference values for antibodies, possibly explains another part of the heterogeneity between studies. For example, reference values for TSH indicating (auto-immune) hypothyroidism varied from >4.0 up to >10 mU/L (48, 49, 50, 51), usually but not always (49, 51, 52) dependent on fT4 levels to determine if the condition was classified as clinical overt or subclinical disease. In most studies, only hypothyroid patients with antibody positivity were considered as having auto-immune hypothyroidism (9, 41, 44, 53, 54, 55, 56, 57) and others included ultrasound to confirm the diagnosis (58) or both (59, 60, 61, 62, 63). Two studies counted cases that were treated for their thyroid disease irrespective of antibodies (12, 64). In ten studies, no information was given on diagnostic criteria at all. Because the prevalence is not always estimated based on antibody positivity, overall prevalence in this meta-analysis is probably slightly overestimated because patients with hypothyroidism other than auto-immune-mediated disease are included in some of the studies.

Hyperthyroidism

We found a prevalence of 1.3% for hyperthyroidism, which is comparable to the general population, as reported prevalence ranges from 1 to 4% (40, 65, 66, 67) Three studies reported a notable high prevalence (10, 68, 69) of hyperthyroidism. One of these studies reported age at onset of diabetes, which was remarkably high (26 years) (70). This is in line with previously published studies that showed a higher age at onset of diabetes in patients with concomitant Graves' disease (71, 72).

It has been shown that the prevalence of hyperthyroidism is depending on the age and sex of the population (65) and more prevalent in woman and older age (71). In this study, we found a mean prevalence of 1.34% percent in woman vs 0.9% in men, although this difference was not significant.

Whereas the prevalence of hyperthyroidism was low, the pooled prevalence of TRAb positivity was approximately seven-fold higher than the disease prevalence (9.5%), meaning that antibody positivity does not implicate clinical overt disease in the majority of cases.

Celiac disease

In our study, the mean prevalence of CD in type 1 diabetes patients was 4.5 to 9-fold higher than that in the general population (73, 74). The reported prevalence was highly depending on diagnostic criteria and intensity of screening. Taking into account patients with active disease only, the pooled prevalence is 4.0%.

Most studies determined the indication for duodenal biopsy based on antibody positivity (58/87 studies, 67%), but various antibodies were used as reference, and as a consequence, the proportion of patients screened with biopsies varied from 0.7 to 100%. The percentage of patients diagnosed with CD increased if more patients underwent a biopsy. Studies that diagnosed CD in all the patients who underwent duodenal biopsy found a mean prevalence of 4.9% (95% CI: 3.4–6.7, 14 studies). These numbers may indicate that accuracy in diagnosis of CD and thereby the magnitude of the celiac iceberg (75) depends on criteria used to select patients for biopsy. Some studies suggest that CD precedes other auto-immune disease, in particular T1D, by increasing gut permeability for gluten (76, 77), which would implicate that CD is mainly established before the diagnoses of T1D and not increasing thereafter. This hypothesis would be supported by previous studies concluding that in half the patients CD is diagnosed within 2 years of T1D diagnosis (78). In our study, any relation with age or diabetes duration would be difficult to demonstrate, as we did not have individual patient data.

Gastric autoimmunity

In this meta-analysis prevalence of parietal cell antibodies was around a twofold higher than the general population, but anemia as a consequence of vitamin B12 deficiency was twenty times more common than usual. This possible discrepancy may be caused by other (non-auto-immune) factors such as comorbidity or metformin use. However, it does confirm the need for regular screening for anemia and vitamin B12 deficiency.

Vitiligo

In our analysis, 13 studies reported prevalence of vitiligo in type 1 diabetes patients. The mean prevalence was 2.4 vs 0.4% in the general population (79). Vitiligo was often registered as secondary finding and screening methods were usually undisclosed (17, 72, 80). This may lead to an underestimation of the prevalence. In studies that screened specifically on AAID, cutaneous manifestations or vitiligo (16, 81, 82, 83, 84) in diabetes patients estimated prevalence was higher, 4.3 vs 1.4%, compared to studies that were not actively screening. Vitiligo therefore, may be a common missed diagnosis in many patients with

type 1 diabetes as it has limited clinical consequences and therefore active screening is frequently absent.

Adrenal gland insufficiency

Auto-immune adrenal gland insufficiency (Addison's disease) is a serious disease, caused by the loss of adrenal function and impaired cortisol production. The most serious and potential lethal manifestation of adrenal insufficiency is shock during a crisis, but it also complicates management of diabetes with increased risk for hypoglycemia or disturbances in the potassium regulation (85, 86). Although in this study the prevalence of adrenal gland insufficiency was low, only 0.2%, this is higher than that in the general population, namely 0.012% (87). Considering the implications concomitant Addison's disease has for T1D patients, this is an important risk to consider.

Toward a screening policy for auto-immune disease in type 1 diabetes

Type 1 diabetes patients are at increased risk for hypothyroidism, CD, pernicious anemia, vitiligo and Addison's disease. Clearly, in the presence of symptoms of any of the auto-immune conditions mentioned, there should be no threshold to test given the increased risk. It is however less obvious whether a screening policy should routinely be implemented in non-symptomatic patients, even though the number needed to screen for the most prevalent condition (thyroid disease) is approximately 100 (71) and for some of the diseases the prevalence increases substantially with age. If more conditions are included in a screening policy, (for example bi-annually) the yield of screening will increase. An important consideration is that some of the conditions have clinical consequences and that concomitant auto-immune disease can be relevant in diabetes regulation. The ultimate decision on screening however requires careful balancing of costs, burden and yield.

Conclusion

The prevalence of auto-immune hypothyroidism, CD, adrenal gland insufficiency, vitiligo and gastric autoimmunity is higher in type 1 diabetes patients. Concomitant auto-immune disease can complicate diabetes management and has various clinical presentations. For this reason, the need for adequate screening protocols seems obvious. The ultimate decision on optimal screening policy remains obscure.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0515.

Declaration of interest
O M Dekkers is a methodological editor of the journal, but was not involved in the review process of this article. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement
Study concept and design: C Nederstigt, O M Dekkers. Acquisition of the data: C Nederstigt, L G M Janssen, B S Uitbeijerse. Analysis and interpretation of the data: C Nederstigt, L G M Janssen, B S Uitbeijerse. Drafting of the manuscript: C Nederstigt, O M Dekkers. Critical revision of the manuscript for important intellectual content: O M Dekkers, E P M Corssmit, L G M Janssen, B S Uitbeijerse, E J P de Koning. Statistical analysis: C Nederstigt, O M Dekkers. Obtained funding: C Nederstigt. Study supervision: O M Dekkers.

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